#### Ventricular arrhythmias due to LV dysfunction or LV dysfunction due to frequent VAs – the hen or the egg?

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### Agenda

- Definition
- Pathophysiology
- Clinical factors for development of LV dysfunction
- Risk stratification
- Drugs vs ablation



#### Arrhythmia induced cardiomyopathy Definitions

- AICM is a condition, in which atrial or ventricular tachyarrhythmias or frequent PVCs result in reversible LV dysfunction and systolic HF
  - PVC-induced CMP (arrhythmia induced)
  - PVCs-worsened CMP (arrhythmia mediated)
- CMP with superimposed PVCs



#### PVCs vs primary cardiomyopathy The old chicken – egg dilema..





#### **EDITORIALS**

#### Tachycardia and Cardiomyopathy: The Chicken-Egg Dilemma Revisited\*

#### JOHN J. GALLAGHER, MD, FACC

Charlotte, North Carolina

The effect of an *acute* increase in heart rate on left ventricular function has been well documented in patients with paroxysmal arrhythmias. There is general agreement that cardiac output remains relatively constant despite a decrease in stroke volume and end-diastolic volume. These changes may be accompanied by minor wall motion abnormalities. Nonetheless, in the absence of other heart disease, initiation of supraventricular tachycardia has not resulted acutely in any overall decrease in ejection fraction compared with baseline function in sinus rhythm (1). Similarly, no appreciable change in ejection fraction has been observed in normal subjects despite atrial pacing to rates of 120 to 160 beats/min (2–4). identify "improvement" is somewhat limited, since the initial measure of left ventricular function may have been artificially low because of a rapid heart rate. Nonetheless, the continued late improvement noted supports the concept that chronic tachycardia may have resulted in a reversible form of cardiomyopathy.

Chronic tachycardia and left ventricular dysfunction. Chronic supraventricular tachycardia was once regarded as a benign process without adverse myocardial sequelae (6,7). Subsequently, however, a relation between incessant tachycardia and cardiomyopathy has been suggested by a number of investigators (8–14). Data from my laboratory support this concept (15). Nine patients (aged 5



## PVCs as the reversible cause of cardiomyopaty

#### **Original Article**



Suppression of Frequent Premature Ventricular Contractions and Improvement of Left Ventricular Function in Patients With Presumed Idiopathic Dilated Cardiomyopathy

DOUGLAS F. DUFFEE, M.D.,\* WIN-KUANG SHEN, M.D., AND HUGH C. SMITH, M.D.

- 14 pts with ectopy >20,000/24 hours and impaired LV EF
- Supression of ectopy (>75%) using amiodarone in 5 pts
- Improvement of LV EF from 27±10% to 49±17% (p<0.05)</li>
- Conclusions: ectopy may be the cause of reversible CMP



Duffee Mayo Clinic proc 1998

### Or by ablation...

#### First Evidence of Premature Ventricular Complex-Induced Cardiomyopathy: A Potentially Reversible Cause of Heart Failure

SUMEET S. CHUGH, M.D., WIN-K. SHEN, M.D., DAVID M. LURIA, M.D., and HUGH C. SMITH, M.D.

From the Cardiovascular Division, Department of Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

**PVC-Induced Cardiomyopathy.** Tachycardia-induced cardiomyopathy is a well-recognized and reversible condition, but left ventricular dysfunction due to frequent isolated premature ventricular complexes (PVCs) has not been reported. We observed resolution of dilated cardiomyopathy in a patient after a focal source of PVCs was eliminated by radiofrequency ablation. In a subset of patients with heart failure, PVC-induced cardiomyopathy may be a potentially reversible cause of left ventricular dysfunction. (J Cardiovasc Electrophysiol, Vol. 11, pp. 328-329, March 2000)

### Pathophysiology

## PVC induced/worsened cardiomyopathy



## **Pulse deficit during PVCs**





## Pathophysiology of AICM



In animal models of PVC induced CMP no evidence of inflammation, apoptosis, fibrosis.

Dyssynchrony during PVC hypothesized as potential mechanism, but CMP may be induced also by PACs

Cha et al Circ EP 2012;5:229-236 Huizar et al Circ EP 2011;4:543-9. Hasdemir et al Europace 2013;15:1790



### Pathophysiology Animal data

- 9 mongrel dogs
- RV apical PVCs (240ms CI)
- Burden 0%, 7%, 14%, 25%, 33%, 50% for 8weeks
- PVC induced CMP in some canines with 25%, 33% but all with 50%
- No changes in BNP and interleukin 6 levels.
- LV systolic function declined linearly as PVC burden increased





# Which clinical factors are associated with PVC induced CMP?



### What level of PVCs is critical?

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- 174 pts with PVCs (24-hour Holter)
- LVEF (mean. 0.37 ± 0.10) in 57 (33%)
- Ablation led to improvement of LVEF



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Baman TS, et al. Heart Rhythm 2010;7:865-869

## Which factors are associated with normalization of EF after ablation?

- Prospective multicenter trial
- 155pts with LV dysfunction and frequent PVCs without known SHD
- 49% had normalization of LVEF
- Factors associated with pure PVC induced CMP:
  - Baseline PVC burden>17%
  - Intrinsic QRS<130ms</li>
  - EDDLV <63mm</p>



Penela et al. Heart Rhythm 2017;14:1864-1870.



#### Other factors influencing significance of VAs Timing, location, symptoms and ...



Interpolated PVBs lead more often to CMP

\*Asymptomatic course, epicardial location of PVCs, retrograde P wave

Sun et al. Int J Cardiovascular Imagning 2003;19:925 \*Ban JE, Europace 2013;15:735-741. \*Blaye-Felice MS, Heart Rhythm 2016;13:103-110.



### **Augmentation of PCWP after PVC**



Kuroki K, et al. Eur J Heart Fail (2012) 14, 1112-1120



## Improvement after ablation was higher in pts with augmentation



- 7.4 + 0.9 months
- Echo parameters and BNP improved in group with augmentation
- PVC coupling interval

   500 ms and
   presence of retrograde
   P wave (PVC-P' interal
   300ms) predicted
   augmentation with
   high sensitivity

Kuroki K, et al. Eur J Heart Fail (2012) 14, 1112–1120



### **Frequent PVCs and CRT**



### PVCs as reason for loss of BiV capture



What is significance of PVCs in CRT recipients?

- Analysis of MADIT CRT study
- Prior implantation 3.2±5.5%
   PVCs/24 hour monitoring
- Patients with >0.1% ectopy beats less chance of reverse remodling and higher risk of HF/death/VA



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Ruwald JACC 2014;64:971

### Frequent PVCs vs CRT

- 65 pts with CRT
- Nonresponders >10,000 PVCs/24hours
- RF ablation of 76 foci
- Improvement after ablation:
  - LV EF 26±5% to 33±7% (p<0.001)</p>
  - LV volume 178±72 to 145±32ml
  - NYHA III to II (p<0.001)</li>
- In mutlivariate analysis improvement of EF in pts with frequent ectopy more than 22%/24 hours



Lakkireddy et al JACC 2012



## Does elimination of PVCs lead to clinically relevent improvement?





## Catheter ablation of ectopy improves LV EF

	Trea	atment		Bas	seline			Mean	Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Fixe	d, 95% CI [%]	IV, Fixed, 95% CI [%]
Ardashev et al, 2011	69.5	2.6	30	61.6	6.4	30	42.4%	7.90	[5.43, 10.37]	
Kim et al, 2010	59.8	7.2	24	51.1	6.6	24	17.0%	8.70	[4.79, 12.61]	*
Wijnmaalen et al, 2010	59	5	23	56	8	23	17.4%	3.00	[-0.86, 6.86]	+
Yarlagadda et al, 2005	62	6	7	39	6	7	6.6%	23.00	16.71, 29.29]	-
Yokokawa et al, 2012	60	4	24	39	9	24	16.7%	21.00 [	17.06, 24.94]	
Total (95% CI)			108			108	100.0%	10.36	[8.75, 11.97]	•
Heterogeneity: $\chi^2 = 62.0$	04, df = 4 (P	< 0.00	001); I <sup>2</sup>	= 94%			1991.0000000			
Test for overall effect: Z	= 12.61 (P	< 0.000	01)							Favours Control Favours Experimenta



Lamba J, et al. PACE 2014, 37: 73-8





## In pts with LV dysfunction may prevent prophylactic implantation of ICD....

- 66pts with frequent PVCs, EF LV <35% suitable for primary prophylactic ICD implantation
- After ablation
  - EF LV improved from 28±4% to 42±12%
  - 42pts (64%) not fulfilled the indication criteria for ICD implant



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#### Penela D Heart Rhythm 2015;12:2434

## Risk stratification of patients with frequent PVCs

- 321 pts undergoing PVC ablation
- SHD detected in 20% by MRI prior ablation
- VT inducible by PES performer during ablation in 5% of pts
- Highest event rate in pts with LGE and positive PES despite "preserved" EF





## Risk stratification of patients with NICM

FIGURE 2 Combined Endpoint of Any Major Adverse Cardiovascular Events

- Metanalysis of LGE siginificance on MRI in pts with NICM
- 34 studies 4.554pts
- LGE present in 45%pts
  - Mortality
    - Odds ratio 3.4 (95% CI 2.0-5.7)
  - Ventricular arrhythmias
    - Odds ratio 4.5 (95% CI 3.4-6.0)
  - Rehospitalization for HF
    - Odds ratio 2.7 (95% CI 1.7-4.2)

16 16 13 15 11 9 19 7 10 133 50 47	35 27 42 18 31 31 72 46 20 142 94	8 3 1 11 10 0 6 1 5 96	66 38 37 14 72 30 112 19 77		6.11 16.97 16.14 1.36 3.41 - 25.76 6.33 3.23 14.40	[2.26; 16.50] [4.16; 69.30] [1.99; 130.72] [0.23; 8.08] [1.26; 9.21] [1.42; 465.99] [2.39; 16.80] [0.37; 28.25]	4.0% 3.1% 2.0% 2.5% 4.0% 1.3% 4.1% 1.9%
16 13 15 11 9 19 7 10 133 50 47	27 42 18 31 31 72 46 20 142 94	3 1 11 10 0 6 1 5 96	38 37 14 72 30 112 19 77		16.97 16.14 1.36 3.41 - 25.76 6.33 3.23 14.40	[4.16; 69.30] [1.99; 130.72] [0.23; 8.08] [1.26; 9.21] [1.42; 465.99] [2.39; 16.80] [0.37; 28.25]	4.0% 3.1% 2.0% 2.5% 4.0% 1.3% 4.1% 1.9%
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10 133 50 47	20 142 94	5 96	77		14 40	[0107] 20120]	
133 50 47	142 94	96			177.771	[4.08: 50.81]	3.4%
50 47	94		330		36.02	[17.61: 73.68]	4.7%
47		24	91		3.17	[1.71: 5.88]	4.9%
	81	4	81		26.61	[8.88: 79.76]	3.8%
12	48	2	24		3.67	[0.75: 17.95]	2.8%
31	61	18	167		8.55	[4.24: 17.24]	4.7%
11	36	2	39		8.14	[1.66: 39.91]	2.8%
37	76	24	61	<b>↓</b> ↓	1.46	[0.74: 2.90]	4.8%
14	61	1	25	F 4	7.15	[0.89; 57.65]	2.0%
4	23	9	41	i	0.75	[0.20: 2.77]	3.3%
11	25	2	32		11.79	[2.30; 60.44]	2.7%
18	122	0	53		18.94	[1.12: 320.44]	1.3%
23	55	5	32		3.88	[1.30; 11.59]	3.8%
31	105	11	102		3.47	[1.63; 7.36]	4.6%
9	21	0	10	↓ <u></u>	15.96	[0.83; 307.94]	1.2%
20	79	19	131	l 🖛 i	2.00	[0.99; 4.03]	4.7%
34	71	3	34		9.50	[2.66; 33.92]	3.4%
16	35	10	50		3.37	[1.29; 8.80]	4.1%
16	66	4	52		3.84	[1.20; 12.31]	3.6%
14	171	14	466		2.88	[1.34; 6.17]	4.6%
40	261	4	104		4.52	[1.58; 12.99]	3.9%
6	22	1	19		6.75	[0.73; 62.24]	1.9%
	1977		2409		5.46	[3.77; 7.91]	100.0%
	31 11 37 14 4 11 18 23 31 9 20 34 16 16 16 14 40 6 5326, <i>p</i> < 1	31       61         11       36         37       76         14       23         11       25         18       122         23       55         31       105         9       21         20       79         34       71         16       35         16       66         14       171         40       261         6       22         1977         5326, $p < 0.01$	31       61       18         11       36       2         37       76       24         14       61       1         4       23       9         11       25       2         18       122       0         23       55       5         31       105       11         9       21       0         20       79       19         34       71       3         16       35       10         16       66       4         14       171       14         40       22       1         1977	31       61       18       167         11       36       2       39         37       76       24       61         14       61       1       25         4       23       9       41         11       25       2       32         18       122       0       53         23       55       5       32         31       105       11       102         9       21       0       10         20       79       19       131         34       71       3       34         16       35       10       50         16       66       4       52         14       171       14       466         40       22       1       19         1977       2409       5326, $p < 0.01$ 50	31       61       18       167         11       36       2       39         37       76       24       61         14       61       1       25         4       23       9       41         11       25       2       32         18       122       0       53         23       55       5       32         31       105       11       102         9       21       0       10         20       79       19       131         34       71       3       34         16       35       10       50         16       66       4       52         14       171       14       466         40       261       4       104         6       22       1       19         1977       2409       0.01       0.1       1       10       100         5326, $p < 0.01$ 0.01       0.1       1       10       100	31       61       18       167       8.55         11       36       2       39       8.14         37       76       24       61       1.46         14       61       1       25       7.15         4       23       9       41       7.15         4       23       9       41       7.15         18       122       0       53       8.88         31       105       11       102       3.47         9       21       0       10       15.96         20       79       19       131       2.00         34       71       3       34       9.50         16       35       10       50       3.37         16       66       4       52       3.84         14       171       14       466       4.52         6       22       1       19       4.52         62       1       19       6.75       5.46         6326, $p < 0.01$ 0.01       0.1       10       100	31       61       18       167       8.55 $[4.24; 17.24]$ 11       36       2       39       8.14 $[1.66; 39.91]$ 37       76       24       61       1.46 $[0.74; 2.90]$ 14       61       1       25       7.15 $[0.89; 57.65]$ 4       23       9       41       0.75 $[0.20; 2.77]$ 11       25       2       32       11.79 $[2.30; 60.44]$ 23       55       5       32       18.94 $[1.12; 320.44]$ 23       55       5       32       3.88 $[1.30; 11.59]$ 31       105       11       102       3.47 $[1.63; 7.36]$ 9       21       0       10       15.96 $[0.83; 307.94]$ 20       79       19       131       2.00 $[0.99; 4.03]$ 34       71       3       34       2.00 $[0.99; 4.03]$ 16       66       4       52 $[1.34; 6.17]$ 4.52         40       261       4       104       4.52 $[1.34; 6.17]$ 40       261       <

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Becker MA JACC Img 2018

### How to supress PVCs?



#### Drugs vs ablation Which is better?

- Retrospective analysis
- 510pts with >10k PVCs treated either by ablation (215pts) or AA drugs (295pts)
- LVEF increased significantly after ablation but not drugs
- Of 121pts with reduced function baseline, LVEF normalized in 47% in ablation, but only in 21% in drug group



### **Drugs vs ablation...**

- Pharmacologic treatment:
  - BB, amiodarone???!
- When to ablate?
  - Monomorphic (bimorphic) morphology

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref. <sup>c</sup>
In patients with frequent symptomatic PVC or NSVT:			
- Amiodarone should be considered.	lla	в	64
<ul> <li>Catheter ablation should be considered.</li> </ul>	lla	в	341– 343
Catheter ablation should be considered in patients with LV dysfunction associated with PVCs.	lla	в	341– 343

	Symptoms -	Symptoms +
Impaired EF -	Watchful waiting	Treatment
Impaired EF +	Treatment	Treatment

Priori S, et al. 2015 ESC Guidelines. EHJ 36 (2015) 2793–2867





#### **PVCs from anteroseptal RVOT** "Easy" target for ablation



SUMMARY

99421 QRS complexes

23796 Ventricular ectopics which represent 23 % of total QRS complexes

0 Supravent ricular ectopics which represent  $\,{<}1\,$  % of total QRS complexes

0 Paced QRS complexes which represent <1 % of total QRS complexes



#### PVCs from anteroseptal RVOT "Easy" target for ablation



#### PVCs from LV summit Not that easy target





- Def.: area between bifurcation of LAD and LCx
- GCV divides this into two parts:
  - Superior inacessible part
  - Inferior part accessible by percutaneous epicardial ablation

T Yamada *Circ EP* 2010;3:616-623.



#### A case of LV summit ectopy **Alcohol ablation of coronary sinus branch**

AXIOM-Artis

W 143 C 127

初143 C 113

AXIOM-Artis





#### Echogenicity in the LV summint after alcohol injection



#### 39-year old female with very frequent "narrow" PVCs nad low LV EF 25%





### **MMEPC**

#### **Multifocal ectopic Purkinje-related premature contractions**

- Mutation in SCN5A gene leading to the abnormal repolarization of Na channel
- Typical ECG pattern of junctional and very frequent PVBs originating from conduction systema associated with LV dysfunction and sudden cardiac death
- Therapy: hydroquinidine





#### 41-year old female with very frequent symptomatic PVCs, three ablation attempts on the papillary muscles





#### Tawil – Andersen syndrom LQT 7

- Mutation of KCNJ2
  - Ventricular ectopy, prolonged
     QT with prominent U wave
  - Low-set ears, small lower jaw (micrognathia), hypertelorism, syndactily, clinodactyly
  - hypokalaemic periodic paralysis
- Treatment:
  - BB, flecainide, ICD



Fig. 1: Showing low set ears, micrognathia and retrognathia





## 35year old female with PVCs during treadmill



## Catecholaminergic polymorphic ventricular tachycardia

285 210

90

06

560 107 285 275 275 210 218 218 540

111

218

- Triggered by physical or emotional stress
- PVCs (bidirectional VT), polymorphic VT, atrial arrhythmias
- Diagnosis: stress test, genetics
- Normal baseline ECG and ECHO



### Conclusions

- PVCs may be unrecognized cause of reversible LV dysfunction
- Pathophysiology of PVC induced CMP is complex and not completely understood
- Elimination of ectopy may result in normalization / improvement of LV EF (in CRT patients enables BiV pacing)
- Catheter ablation is more effective than drugs and should be indicated for patients at risk
- In-depth evaluation (including MR imaging + PES) may be used for identification patients at highest risk





## When PVCs may lead to CMP?

#### • Frequency:

- Threshold is not clearly defined
  - >10-20,000 PVCs/24hours, or >20% beats/24 hours,
- Baman Heart Rhythm 2010;7:865
  - Frequency of >24% beats has 79% sensitivity and 78% specificity for impairing LV EF

99421 QRS complexes

23796 Ventricular ectopics which represent 23 % of total QRS complexes

#### • PVCs origin:

- 0 Supraventricular ectopics which represent 1 % of total QRS complexes
   0 Paced QRS complexes which represent <1 % of total QRS complexes</li>
- Ectopy from RV has higher hemodynamic impact than ectopy from LV (similarly with QRS>140ms)
- Munoz JCE 2011;22:791
  - PVCs are significant if from RV>10,000 or from LV>20,000

